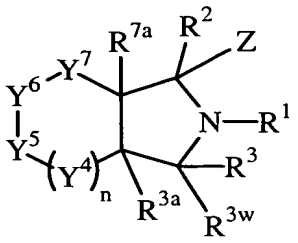
CLAIMS

What is claimed is:

1. A compound of Formula I



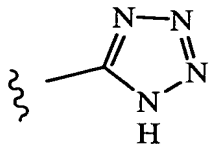
I

or a pharmaceutically acceptable salt thereof,

wherein:

Z is selected from COOH, $C(O)N(H)R^9$, and Z^1;

Z^1 is selected from: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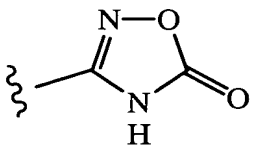
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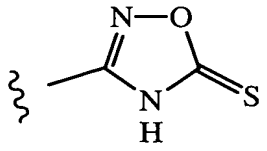
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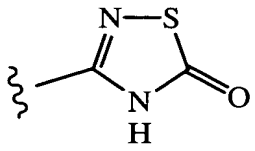
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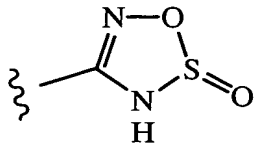

;

Each Y^4, Y^5, Y^6, and Y^7 is $C(R^{10})R^{10w}$; or

One of Y^4, Y^5, Y^6, and Y^7 is selected from O, S, S(O), $S(O)_2$, and NR^5, and the other three of Y^4, Y^5, Y^6, and Y^7 are each $C(R^{10})R^{10w}$; or

Two nonadjacent Y^4, Y^5, Y^6, and Y^7 are independently selected from O, S, S(O), $S(O)_2$, and NR^5, and the other two of Y^4, Y^5, Y^6, and Y^7 are each $C(R^{10})R^{10w}$;

Each R^2, R^3, R^{3w}, R^{3a}, R^{7a}, R^{10}, and R^{10w} is independently selected from:

H, HO, H_2N, $H_2NS(O)_2$-$(G)_m$, HS, Halo, CN, CF_3, $FC(H)_2O$, $F_2C(H)O$, CF_3O, and

a group, which may be unsubstituted or substituted, independently selected from:

C_1-C_6 alkyl-$(G)_m$–, C_2-C_6 alkenyl-$(G)_m$–, C_2-C_6 alkynyl-$(G)_m$–, 2- to 6-membered heteroalkyl-$(G)_m$–, 2- to 6-membered heteroalkenyl-$(G)_m$–, C_3-C_7 cycloalkyl-$(G)_m$–, C_3-C_7 cycloalkenyl-$(G)_m$–, C_7-C_{10} bicycloalkyl-$(G)_m$–, 3- to 7-membered heterocycloalkyl-$(G)_m$–, 7- to 10-membered heterobicycloalkyl-$(G)_m$–, Phenyl-$(G)_m$–, Naphthyl-$(G)_m$–, 5- and 6-membered heteroaryl-$(G)_m$–, 8- to 10-membered heterobiaryl-$(G)_m$–, and

any of the above R^2, R^3, R^{3w}, R^{3a}, R^{7a}, R^{10}, and R^{10w} groups each independently substituted on carbon or nitrogen atoms with from 1 to 6 substituents R^X;

wherein R^3 and R^{3w}, and any geminal pair of R^{10} and R^{10w}, and any two R^X substituents geminally substituted on a carbon atom in substituted R^2, R^3, R^{3w}, R^{3a}, R^{7a}, R^{10}, and R^{10w} groups further may independently be taken together with a carbon atom to which they are both bonded to form the group C(=O);

R^1 is HO or a group that may be unsubstituted or substituted, independently selected from:

C_1-C_6 alkyl-$(T)_m$–, C_2-C_6 alkenyl-$(T)_m$–, C_2-C_6 alkynyl-$(T)_m$–, 2- to 6-membered heteroalkyl-$(T)_m$–, 2- to 6-membered heteroalkenyl-$(T)_m$–, C_3-C_7 cycloalkyl-$(T)_m$–, C_3-C_7 cycloalkenyl-$(T)_m$–, C_7-C_{10} bicycloalkyl-$(T)_m$–, 3- to 7-membered heterocycloalkyl-$(T)_m$–, 7- to 10-membered heterobicycloalkyl-$(T)_m$–, Phenyl-$(T)_m$–, Naphthyl-$(T)_m$–, 5- and 6-membered heteroaryl-$(T)_m$–, 8- to 10-membered heterobiaryl-$(T)_m$–, and

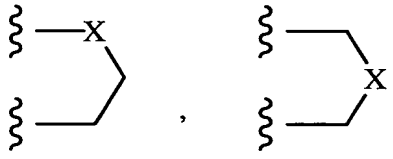
any of the above R^1 groups independently substituted on a carbon or nitrogen atom, with from 1 to 6 substituents R^X;

R^1 may further be H when: (i) at least one of R^2, R^3, R^{3w}, R^{3a}, R^{7a}, R^{10}, and R^{10w} is not H, or (ii) Z is C(O)N(H)R^9 wherein R^9 is as defined above wherein m is 1 and L is $S(O)_2$, or (iv) Z is Z^1;

Each R^5 and R^9 is independently H, HO, or a group, which may be unsubstituted or substituted, independently selected from: C_1-C_6 alkyl-$(L)_m$–, C_2-C_6 alkenyl-$(L)_m$–, C_2-C_6 alkynyl-$(L)_m$–, 2- to 6-membered heteroalkyl-$(L)_m$–, 2- to 6-membered heteroalkenyl-$(L)_m$–, C_3-C_7 cycloalkyl-$(L)_m$–, C_3-C_7 cycloalkenyl-$(L)_m$–, C_7-C_{10} bicycloalkyl-$(L)_m$–, 3- to 7-membered heterocycloalkyl-$(L)_m$–, 7- to 10-membered heterobicycloalkyl-$(L)_m$–, Phenyl-$(L)_m$–, Naphthyl-$(L)_m$–, 5- and 6-membered heteroaryl-$(L)_m$–, 8- to 10-membered heterobiaryl-$(L)_m$–, and any of the above R^5 and R^9 groups independently substituted, on carbon or nitrogen atoms, with from 1 to 6 substituents R^X;

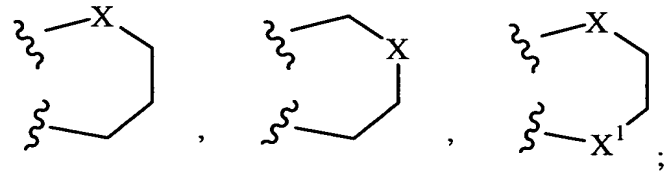
wherein any 2 groups each selected from R^5, R^{10}, and R^{10w} that are bonded to contiguous carbon or nitrogen atoms in Formula I may be taken together with the contiguous atoms in Formula I to which they are bonded to form C=C or C=N;

wherein any 2 groups selected from R^1, R^2, R^3, R^{3w}, R^{3a}, R^5, R^{7a}, R^{10}, and R^{10w} that are bonded to contiguous carbon or nitrogen atoms in Formula I may be taken together to form (i) a diradical selected from CH_2 and $CH_2CH_2CH_2$, (ii) a 3-membered diradical selected from:



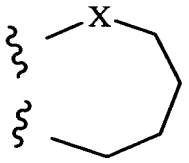
, or

(iii) a 4-membered diradical selected from:



;

wherein any two groups R^3 and R^{3w}, and R^{10} and R^{10w}, that are geminally bonded to a single carbon atom in Formula I may be taken together to form a 4-membered diradical as defined above or a 5-membered diradical selected from:



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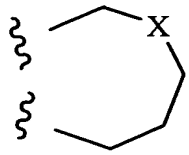

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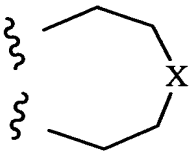

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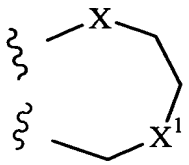


;

wherein any 2 groups selected from R^1, R^2, R^3, R^{3w}, R^{3a}, R^5, R^{7a}, R^{10}, and R^{10w} that are bonded to noncontiguous carbon or nitrogen atoms in Formula I may be taken together to form (i) a CH_2CH_2 diradical or (ii) -O- diradical;

X is O, S, S(O), $S(O)_2$, or N-R;

X^1 is O or N-R;

Each G is independently selected from C(=O), S(O), $S(O)_2$, OC(O), $N(R^4)C(O)$, $(C_1\text{-}C_8$ alkylenyl$)_m$, (2- to 8-membered heteroalkylenyl$)_m$, and $(C_1\text{-}C_8$ alkylenyl$)_m$ and (2- to 8-membered heteroalkylenyl$)_m$ independently substituted on carbon or nitrogen atoms with from 1 to 4 substituents R^X;

Each T is independently selected from S(O), $S(O)_2$, $N(R^4)C(O)$, $(C_1\text{-}C_8$ alkylenyl$)_m$, (2- to 8-membered heteroalkylenyl$)_m$, and $(C_1\text{-}C_8$ alkylenyl$)_m$ and (2- to 8-membered heteroalkylenyl$)_m$ independently substituted on carbon or nitrogen atoms with from 1 to 4 substituents R^X;

Each L is independently selected from O, $N(R^4)$, S(O), $S(O)_2$, C(=O), C(O)O, OC(O), $C(O)N(R^4)$, $N(R^4)C(O)$, $OC(O)N(R^4)$, $N(R^4)C(O)O$, $N(R^4)C(O)N(R^{4w})$, $(C_1\text{-}C_8$ alkylenyl$)_m$, (2- to 8-membered heteroalkylenyl$)_m$, and $(C_1\text{-}C_8$ alkylenyl$)_m$ and (2- to 8-membered heteroalkylenyl$)_m$ independently substituted on carbon or nitrogen atoms with from 1 to 4 substituents R^X;

Each R, R^4, and R^{4w} is independently H or C_1-C_6 alkyl, which C_1-C_6 alkyl may be unsubstituted or substituted with from 1 to 3 substituents R^X;

Each R^X is independently selected from: HO, H_2N, $H_2NS(O)_2$, CN, CF_3, FCH_2O, $F_2C(H)O$, CF_3O, O_2N, C_1-C_6 alkyl-$(Q)_m$–, 2- to 6-membered heteroalkyl-$(Q)_m$–, C_3-C_7 cycloalkyl-$(Q)_m$–, 3- to 7-membered heterocycloalkyl-$(Q)_m$–, Phenyl-$(Q)_m$, and 5-membered heteroaryl-$(Q)_m$,

wherein phenyl and 5-membered heteroaryl-$(Q)_m$ each is unsubstituted or independently substituted with from 1 to 3 substituents selected from halo, HO, HOC(O), $CH_3OC(O)$, $CH_3C(O)$, H_2N, CF_3, CN, and C_1-C_6 alkyl;

wherein each R^X substituent on a carbon atom may further be independently selected from: HS, (C_1-C_6 alkyl)-S, halo, and HO_2C; and

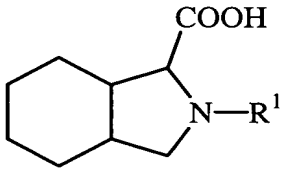
Each Q independently is O, $N(R^6)$, S(O), $S(O)_2$, C(=O), C(O)O, OC(O), $C(O)N(R^6)$, $N(R^6)C(O)$, $OC(O)N(R^6)$, $N(R^6)C(O)O$, or $N(R^6)C(O)N(R^{6w})$;

Each R^6 and R^{6w} independently is H or unsubstituted C_1-C_6 alkyl;

Each m independently is an integer of 0 or 1; and

Each n independently is an integer of from 0 to 2.

2. The compound according to Claim 1 of Formula II



II

or a pharmaceutically acceptable salt thereof,

wherein R^1 is HO or a group that may be unsubstituted or substituted, independently selected from:

C_1-C_6 alkyl-$(T)_m$–, C_2-C_6 alkenyl-$(T)_m$–, C_2-C_6 alkynyl-$(T)_m$–, 2- to 6-membered heteroalkyl-$(T)_m$–, 2- to 6-membered heteroalkenyl-$(T)_m$–, C_3-C_7 cycloalkyl-$(T)_m$–, C_3-C_7 cycloalkenyl-$(T)_m$–, C_7-C_{10} bicycloalkyl-$(T)_m$–, 3- to 7-membered heterocycloalkyl-$(T)_m$–, 7- to 10-membered heterobicycloalkyl-$(T)_m$–, Phenyl-$(T)_m$–, Naphthyl-$(T)_m$–, 5- and 6-membered heteroaryl-$(T)_m$–, 8- to 10-membered heterobiaryl-$(T)_m$–, and

any of the above R^1 groups independently substituted on a carbon or nitrogen atom, with from 1 to 6 substituents R^X;

Each T is independently selected from S(O), $S(O)_2$, $N(R^4)C(O)$, (C_1-C_8 alkylenyl)$_m$, (2- to 8-membered heteroalkylenyl)$_m$, and (C_1-C_8 alkylenyl)$_m$ and (2- to 8-membered heteroalkylenyl)$_m$ independently substituted on carbon or nitrogen atoms with from 1 to 4 substituents R^X;

Each R^4 is independently H or C_1-C_6 alkyl, which C_1-C_6 alkyl may be unsubstituted or substituted with from 1 to 3 substituents R^X;

Each R^X is independently selected from: HO, H_2N, $H_2NS(O)_2$, CN, CF_3, FCH_2O, $F_2C(H)O$, CF_3O, O_2N, C_1-C_6 alkyl-$(Q)_m$–, 2- to 6-membered heteroalkyl-$(Q)_m$–, C_3-C_7 cycloalkyl-$(Q)_m$–, 3- to 7-membered heterocycloalkyl-$(Q)_m$–, Phenyl-$(Q)_m$, and 5-membered heteroaryl-$(Q)_m$,

wherein phenyl and 5-membered heteroaryl-$(Q)_m$ each is unsubstituted or independently substituted with from 1 to 3 substituents selected from halo, HO, HOC(O), $CH_3OC(O)$, $CH_3C(O)$, H_2N, CF_3, CN, and C_1-C_6 alkyl;

wherein each R^X substituent on a carbon atom may further be independently selected from: HS, (C_1-C_6 alkyl)-S, halo, and HO_2C; and

Each Q independently is O, $N(R^6)$, S(O), $S(O)_2$, C(=O), C(O)O, OC(O), $C(O)N(R^6)$, $N(R^6)C(O)$, $OC(O)N(R^6)$, $N(R^6)C(O)O$, or $N(R^6)C(O)N(R^{6w})$;

Each R^6 and R^{6w} independently is H or unsubstituted C_1-C_6 alkyl; and
Each m independently is an integer of 0 or 1.

3. The compound according to Claim 2, wherein R^1 is unsubstituted or substituted C_1-C_6 alkyl-$(L)_m$.

4. The compound according to Claim 1, selected from:
1,2–dimethyl–octahydro–isoindole–1–carboxylic acid hydrochloride;
1–methyl–octahydro–isoindole–1–carboxylic acid hydrochloride;
5,6-Dimethoxy-octahydro-isoindole-1-carboxylic acid;
cis-2,3,3a,4,7,7a-Hexahydro-1*H*-isoindole-1-carboxylic acid hydrochloride;
diastereomer 1 of 6-chloro-2,2-dimethyl-octahydro-[1,3]dioxolo[4,5-*f*]isoindole-5-carboxylic acid; and
diastereomer 2 of 6-chloro-2,2-dimethyl-octahydro-[1,3]dioxolo[4,5-*f*]isoindole-5-carboxylic acid; or
a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 selected from:
3–aza–6–oxabicyclo[4.3.0]nonane–2–carboxylic acid;
10–oxa–4–aza–tricyclo[5.2.1.$0^{2,6}$]decane–3–carboxylic acid;
4–methyl–4–aza–tricyclo[5.2.2.$0^{2,6}$]undecane–3–carboxylic acid hydrochloride; and
4–aza–tricyclo[5.2.2.$0^{2,6}$]undecane–3–carboxylic acid hydrochloride; or
a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1, selected from:
3–aza–6,6–difluorobicyclo[3.3.0]octane–2–carboxylic acid;
3–aza–6–fluorobicyclo[3.3.0]octane–2–carboxylic acid;
3–aza–6–*n*–butoxybicyclo[3.3.0]octane–2–carboxylic acid;
3–aza–6–hydroxybicyclo[3.3.0]octane–2–carboxylic acid hydrochloride;
3–aza–6–oxobicyclo[3.3.0]octane–2–carboxylic acid hydrochloride;
octahydro–pyrrolo[2,1–*a*]isoindole–9b–carboxylic acid hydrochloride; or

a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 1, selected from:
7*a*-benzyl-octahydro-isoindole-1-carboxylic acid hydrochloride;
7*a*-methyl-octahydro-isoindole-1-carboxylic acid;
3,3-dimethyloctahydro-isoindole-1-carboxylic acid hydrochloride;
3–(octahydro–isoindol–1–yl)–4*H*–[1,2,4]oxadiazol–5–one; and
3–(2–methyl–octahydro–isoindol–1–yl)–4*H*–[1,2,4]oxadiazol–5–one; or
a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

9. A pharmaceutical composition, comprising a compound according to Claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

10. A method of treating joint cartilage damage, osteoarthritis, rheumatoid arthritis, or joint inflammation, or alleviating joint pain, in a mammal suffering from joint cartilage damage, osteoarthritis, rheumatoid arthritis, joint inflammation, or joint pain, respectively, comprising administering to the mammal a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

11. A method of treating joint cartilage damage, osteoarthritis, rheumatoid arthritis, or joint inflammation, or alleviating joint pain, in a mammal suffering from joint cartilage damage, osteoarthritis, rheumatoid arthritis, joint inflammation, or joint pain, respectively, comprising administering to the mammal a compound according to Claim 2, or a pharmaceutically acceptable salt thereof.